MH

CERTIFICATE OF MAILING
I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE WITH SUFFICIENT POSTAGE AS FIRST-CLASS MAIL IN AN ENVELOPE ADDRESSED TO: ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231, ON 14 March 2002

ATTORNEY FOR APPLICANT

3/14/02
DATE

0 0350 #3 0400 0350 02-28-02

Attorney Docket No.: P51223

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	McAllister et al.	14 March 2002
Serial No.:	10/060,849	Group Art Unit: Unknown
Filed:	30 January 2002	Examiner: Unknown
For:	Pharmaceutical Formulation	

Assistant Commissioner for Patents
Washington, D.C. 20231

SUBMISSION OF PRIORITY DOCUMENTS

Sir:

Pursuant to the requirements of 37 CFR §1.55 please find enclosed herewith a certified copy of Applicants foreign provisional application, Great Britain Patent 0102342.3. This submission is believed to meet all the requirements for a claim to priority under 35 USC §119 in the above noted application. This submission and the claim to priority have been made within the 4 month time frame from filing.

If the Examiner has any questions or comments on this matter, please contact the undersigned at the number indicated below.

It is not believed that any fees or charges are associated with this submission. However, if this is not the case, the Commissioner is hereby authorized to debit Account No. 19-2570 accordingly.

Respectfully submitted,

Dara L. Dinner
Attorney for Applicants
Registration No. 33,680

GLAXOSMITHKLINE
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939
Phone (610) 270-5017
Facsimile (610) 270-5090
N:\DLD\OA\US\51223\submission.doc

PATENTS • DESIGNS • COPYRIGHT • TRADE MARKS
The Patent Office

INVESTOR IN PEOPLE

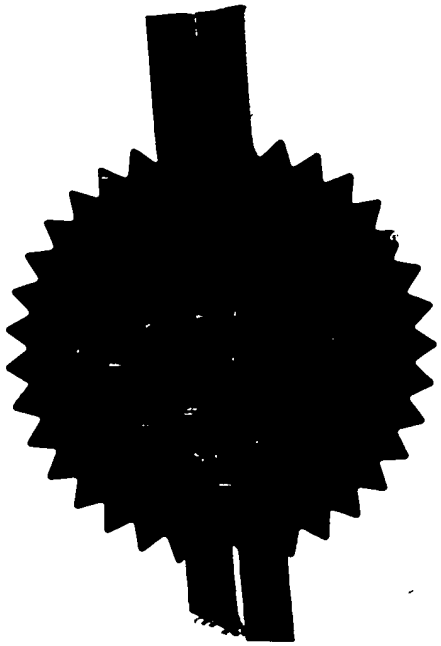
The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed Stephen Hardy

Dated 5 March 2002

CERTIFIED COPY OF PRIORITY DOCUMENT

ents Form 1/77

Patents Act 1977
(Rule 16)

THE PATENT OFFICE
A
30 JAN 2001
LONDON

The Patent Office

1/77

31JAN01 E601927-1 C69803
P01/7700 0.00-0102342.3

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

30 JAN 2001

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — RFW/EB/P51223

2. Patent application number
(The Patent Office will fill in his part) — 0102342.3

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

SmithKline Beecham p.l.c.
New Horizons Court, Brentford, Middx TW8 9EP,
Great Britain

Patents ADP number *(if you know it)* 5800974002

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — Pharmaceutical Formulation

5. Name of your agent *(if you have one)* — Corporate Intellectual Property

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

GlaxoSmithKline
Two New Horizons Court
BRENTFORD
Middlesex TW8 9EP

Patents ADP number *(if you know it)* 08072555001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

Patents Form 1/77

Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	37
Claim(s)	12
Abstract	
Drawings	6

10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request ~~the~~ grant of a patent on the basis of this application

Signature _____ Date 30-Jan-01

R F Walker

12. Name and daytime telephone number of person to contact in the United Kingdom: R F Walker 020 89756336

Warning

After an application for a Patent has beeen filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed tf it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission unless an application has been filed at least six weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505
b) Write your answers in capital letters using black ink or you may type them.
c) If there is not enough space for all relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.
f) For details of the fee and ways to pay please contact the Patent Office.

PHARMACEUTICAL FORMULATION

FIELD OF THE INVENTION

This invention relates to the preparation of an injection molded single or multi-component dosage forms using pharmaceutically acceptable polymeric blends.

BACKGROUND OF THE INVENTION

Various types of pharmaceutical dosage forms are known for oral dosing. Pharmaceutical capsules are well known, generally being intended for oral dosing. Such capsules generally comprise an envelope wall of a pharmaceutically acceptable, e.g. orally ingestible, polymer material such as gelatin, although other materials for capsule walls, e.g. starch and cellulose based polymers are also known. Such capsules generally have soft walls made by making a film on a capsule former, which is then allowed to dry. Rigid walled capsules made by injection molding are also known, see for example US Patents 4,576,284; US 4,591,475; US 4,655,840; US 4,738,724; US 4,738,817 and US 4,790,881 (all to Warner Lambert). These disclose specific constructions of capsules made of gelatin, starch and other polymers, and methods of making them by injection molding of hydrophilic polymer – water mixtures. US Patent 4,576,284 specifically discloses such capsules provided with a cap which closes the capsule, and which is formed in situ on the filled capsule by molding. US Patent 4,738,724 discloses a wide range of rigid capsule shapes and parts.

Multi-compartment capsules, including those of the type where each compartment has different drug release characteristics, or for example, contains a different drug substance or formulation are also known, for example in US 4,738,724 (Warner-Lambert); US 5,672,359 (University of Kentucky); US 5,443,461 (Alza Corp.); WO 95/16438 (Cortecs Ltd.); WO 90/12567 (Helminthology Inst.); DE-A- 3727894, and BE 900950 (Warner Lambert); FR 2524311, and NL 7610038 (Tapanhony NV); FR 1,454,013 (Pluripharm); US 3,228,789 (Glassman); and US 3,186,910 (Glassman)

among others. US 4,738,817 discloses a multicompartment capsule with a similar construction to those of US 3,228,789 and US 3,186,910, made of a water-plasticized gelatin. US 4,738,817 Witter et al., US 4,790, 881, Wittwer et al., and EP 0 092 908, Wittwer, F., all discloses injection molded capsules prepared with gelatin and other excipients. Wittwer et al.'817 a nd '881 also prepare capsules with other hydrophilic polymers, suchas hydroxypropylmethylcellulose phthalate (HPMCP),methylcellulose, microcrystalline cellulose, polyethylene glycol, cellulose acetate phthalate (CAP) and with polyvinylpyrrolidone. Both US 4,790,881 and EP 0 091 908 propose other polymers having enteric properties suitable for use, including generally acrylates and methacrylates (Eudragits) although none are demonstrated and no specific details are provided.

Pharmaceutical dosage forms are also known which comprise a matrix of a solid polymer, in which a drug substance is dispersed, embedded or dissolved as a solid solution. Such matrixes may be formed by an injection molding process. This technology is discussed in Cuff G, and Raouf F, Pharmaceutical Technology, June (1998) pages 96-106. Some specific formulations for such dosage forms are disclosed in US 4,678,516; US 4,806,337; US 4,764,378; US 5,004,601; US 5,135,752; US 5,244,668; US 5,139,790; US 5,082,655; US 5,552,159; US 5,939,099; US 5,741,519; US 4,801,460; US 6,063,821; WO 99/27909; CA 2,227,272; CA 2,188,185; CA 2,211,671; CA 2,311,308; CA 2,298,659; CA 2,264,287; CA 2,253,695; CA 2,253,700; and CA 2,257,547 among others.

US Patent 5,705,189, is directed to a group of co-polymers of methacrylic acid, methyl methacrylate and methyl acrylate, for use as thermoplastic agents in the production of drugs coatings, and capsules. No information is presented on the quality of the capsule formation with respect to warping or other distortions produced by the injection molding process. Nor is shear rate data presented for the viscosity/temperature figures of the emulsions presented therein.

It is an object of this invention to provide an alternative and improved pharmaceutical dosage form which provides inter alia greater flexibility in the dosage form adapted to a patient's specific administration requirement, and to ease of manufacture. Other objects and advantages of the invention will be apparent from the following description.

It would also be desirable to prepare a pharmaceutical dosage form in which a pharmaceutically acceptable polymeric blend is extruded by hot melt, or injection molded into a suitable dosage form, which may be multicompartmental, such as a capsule. This pharmaceutical polymeric composition as the dosage form, may provide differing physio-chemical characteristics for each segment containing an active agent, such that a convenient dosage form can be optioned which may include a rapid dissolve, immediate, delayed, pulsatile, or modified release which can be produced by simply selecting the appropriate polymer(s) to be molded for each section.

SUMMARY OF THE INVENTION

The present invention provides pharmaceutical compositions, injection moulded capsule shells, linkers, spacers, multicomponent injection moulded capsule shells, linkers or spacers, multicomponent pharmaceutical dosage forms, and other aspects as defined in the claims and description of this application.

One object of the present invention is a process of producing a multicomponent dosage form comprising a pharmaceutically acceptable polymeric blend by injection molding. These multicomponent dosage forms are suitable for containing a pharmaceutically acceptable active agent, or agents, for release thereby.

The present invention is also directed to the novel formulation or composition of a pharmaceutically acceptable polymer and suitable excipients to be used for injection molding of the capsules or multicomponent dosage forms.

Another embodiment of the present invention is directed to the solid dosage form comprising a capsule compartment bounded by a wall made of a pharmaceutically acceptable polymeric formulation/composition, and optionally containing a drug substance.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 - shows injection-molded components comprising Eudragit 4135F 75%, Explotab 20%, stearyl alcohol 5%.

Figure 2 - shows injection-molded components comprising Eudragit 4135F 73%, Pharmacoat 603 10% , Lactose 5%, stearyl alcohol 12%.

Figure 3 - shows injection-molded components comprising Eudragit E100 75%, PolyOx N-80 WSR 20%, stearyl alcohol 5%.

Figure 4 - demonstrates a dissolution profile of the polymeric composition of Eudragit 4135F 75%, Explotab 20%, stearyl alcohol 5%, the shells welded to Eudragit 4135F linkers, , the dissolution media used was pH 7.5 Simulated Intestinal Fluid.

Figure 5 - demonstrates a dissolution profile of the polymeric composition of Eudragit 4135F 73%, Pharmacoat 603 10%, Lactose 5%, stearyl alcohol 12%, with the shells welded to 4135F12% stearyl alcohol linkers, the dissolution media used was pH 7.5, Simulated Intestinal Fluid.

Figure 6 - demonstrates a dissolution profile of the polymeric composition of Eudragit E100 75%, PolyOx N-80 WSR 20%, stearyl alcohol 5%, welded to Eudragit 4135F linkers, the dissolution media used was pH1.2 Simulated Gastric Fluid.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to novel compositions of a pharmaceutically acceptable polymer and excipients, which polymeric composition may be injection molded into one or more components which can be utilized together, such as in a stacked or multicomponent dosage form. It is recognized that the polymeric blends may be injection molded into a single component that may also contain the active agent for oral administration.

The pharmaceutically acceptable polymeric blends as a final dosage form may be designed to provide rapid dissolution, immediate, delayed, or modified dissolution, such as sustained and /or pulsatile release characteristics.

It is one object of the present invention to provide a final dosage form containing a pharmaceutically acceptable drug in a pharmaceutically acceptable polymeric blended multicomponent dosage form.

The parts of the dosage form of this invention, e.g. a capsule compartment wall, a solid sub-unit, or a closure or linker, may comprise a pharmaceutically acceptable polymeric blend (and adhesive material if adhesive welds are formed) which is generally regarded as safe, e.g. for oral ingestion and is capable of being formed into the required shape of a capsule compartment wall, a solid sub-unit, or a closure or linker as described above. A preferred method of forming the polymer material into the desired shape is injection molding, which may be a hot or cold runner injection molding process. Suitable injection molding machines for such a process are known.

The pharmaceutical dosage form may comprises a plurality of capsule compartments each bounded and physically separated from at least one adjacent compartment by a wall made of a pharmaceutically acceptable polymer material, adjacent

compartments being connected together in the assembled dosage form and being retained together by the connection at least prior to administration to a patient, one or more of the compartments containing a drug substance.

Suitably in the assembled dosage form of this first embodiment there are at least two, for example three, such capsule compartments. Three or more such compartments may be linearly disposed in the assembled dosage form, e.g. in an arrangement comprising two end compartments at opposite ends of the line, and one or more intermediate compartments. Suitably there may be two such capsule compartments. Suitably one of such two capsule compartments may be made of a material which is a sustained release component, i.e. so that the capsule compartment wall dissolves, bursts or is otherwise breached to release its contents after a time delay, e.g. when the compartment has reached the intestine. Suitably the other of such two capsule compartments may be made of a material which is an immediate release component, i.e. so that the capsule compartment wall dissolves, bursts or is otherwise breached to release its contents immediately or effectively immediately, e.g. when the compartment is in the mouth or stomach.

One or more, e.g. all, of the capsule compartments may for example be substantially cylindrical, which term includes shapes which have a circular, oval or oblate circular cross section across the longitudinal axis, and shapes which have parallel or tapering e.g. with side walls which taper conically over at least part of their extent. Such substantially cylindrical capsule compartments may be provided with connectable parts at one or both of their longitudinally disposed ends so that the assembled dosage form may also be overall of a substantially cylindrical shape.

A preferred form of the multi-component dosage form of this invention comprises two capsule compartments.

The invention also provides individual sub-units, e.g. individual capsule compartments or solid sub-units adapted for use in the assembled dosage form.

In the assembled dosage form the adjacent capsule compartments may be connected together by means of a weld at the area where two adjacent parts of the dosage form, e.g. sub-units, are in contact, e.g. a thermal weld, an ultrasonic or inductive weld, or an adhesive weld (e.g. curable adhesives such as UV curable adhesive). A thermal

weld may for example be achieved by bringing sub-units into adjacent contact and applying localised heating for example produced by directing a laser beam or a fine jet of hot gas e.g. nitrogen at the area where two adjacent sub-units are in contact. In thermal, inductive and ultrasonic welding normally localised fusion together of the materials of adjacent parts of the dosage form which are in contact occurs, and on subsequent solidification of the materials a bond is formed between the adjacent parts. An adhesive weld may be achieved by applying an adhesive (e.g. curable adhesives such as UV curable adhesive) to parts of the dosage form which when the dosage form is assembled are in contact, and then causing or allowing the adhesive to set.

The multi-component dosage form of the present invention is particularly suited to fabrication using ultrasonic welding.

Ultrasonic welding is a known technique involving the use of high frequency sound energy to soften or melt a thermoplastic material at the site where a joint with the material is required. A general description of ultrasonic welding is for example to be found in the publication "Ultrasonic Welding of Thermoplastics" (TWI Ltd., Abington, Cambridgeshire GB, (1997)). Parts to be joined are held together under pressure and then subjected to ultrasonic vibrations usually at a frequency of 20 – 40 kHz. The actual mechanism responsible for the generation of heat at the joint site is not well understood. An ultrasonic welding machine comprises five main components, being a power supply, a control system, a welding head, fixturing to hold the parts to be welded, and a system to apply the required pressure. The power supply converts electricity into high frequency electric power which drives a transducer, e.g. a piezoelectric transducer, which converts electrical energy, e.g. from the mains supply, into mechanical, i.e. ultrasonic, energy. Between the transducer and the parts to be welded is located a booster and horn system, being a usually metallic component which serves to amplify the ultrasonic waves (the booster horn), transmit the clamping pressure, and deliver the sound energy to the part to be welded (the sonotrode or welding horn). For successful ultrasonic welding careful design of the parts to be welded and set up of the welding equipment is important.

Preferably, additionally or alternatively adjacent sub-units may be provided with respectively inter-connectable first and second connectable parts such that the first connectable part on one sub-unit may connect with the second connectable part on an adjacent part of the dosage form, e.g. an adjacent sub-unit in a suitable configuration, e.g. in the above-mentioned linear configuration. This interconnection may contribute to the strength of bond achieved by the weld, or additionally or alternatively may help to hold adjacent parts of the dosage form together prior to and in readiness for the weld to be formed and contributes to the retention of the adjacent sub-units together, e.g. via a retaining friction, snap, screw or other kind of fit between the connectable parts. The connectable parts may be such as to facilitate the assembly together of the sub-units in preferred configurations, e.g. the connectable part(s) on one or more one sub-unit may be such as to only connect with a corresponding connectable part on other selected sub-units but not with non-corresponding connectable parts on other sub-units. Alternatively the connectable parts on the sub-units may be common and interchangeable so that the sub-units may be connected together in a wide range of combinations. This means inter alia that otherwise different capsule compartments or solid sub-units may have mutually connectable parts so that the different capsule compartments or solid sub-units may be connected together in different combinations of solid sub-units or solid sub-units and capsule compartments.

For example in one embodiment the respective first and second connectable parts may be respectively interlocking parts. For example the first or second part may be a socket part, and the corresponding second or first connectable part may be a corresponding plug part which fits into the socket with a retaining friction, snap, screw or other kind of interlocking fit. If for example these plug and socket parts are common then any plug part on any solid sub-unit or capsule compartment may interconnect with any socket part on another solid sub-unit or capsule compartment.

In a friction fit for example the plug part may be slightly larger than the socket such that force needs to be applied against the natural resilience and contact friction of the plug and socket parts to cause the plug part to enter the socket, and similar force needs to be applied to separate them. In a snap fit for example the plug

and socket parts may be respectively provided with a concavity and a corresponding convexity, such as a ridge and groove, which lock together as the parts are forced together against the natural resilience of the parts. Such a ridge and groove may for example comprise a co-operating circumferential or part circumferential bead and groove, for example located about the circumference of a connectable plug and socket part.

The above-described first and second connectable parts facilitate assembly of sub-units together in various ways.

For example in a dosage form of the invention comprising a linear disposition of three or more e.g. four, sub-units, an intermediate sub-unit may be provided with one or more connectable parts for example one at each end, which may connect with one or more connectable part on an adjacent intermediate sub-unit. An end sub-unit may be provided with one or more connectable part which may connect with a connectable part on an adjacent intermediate sub-unit and/or with one or more connectable part on another end sub-unit. By means of this two end sub-units may connect together in a dosage form comprising two sub-units, or two end sub-units may be connected to one or more intermediate sub-units. By using common first and second connectable parts on the sub-units the various end and intermediate sub-units may be made such that they may be connected together in various combinations of assembled dosage forms.

One or more sub-unit which is a capsule compartments may for example be substantially tub-shaped, i.e. having a base closed by a base wall, and side walls extending from the base wall (herein referred to as an "upward" direction), and an upper open mouth. With such a construction capsule compartments may connect together by the base of a first compartment fitting into the open mouth of an adjacent second capsule compartment, so as to close the mouth of the adjacent capsule compartment, and such that the base wall of the first compartment physically separates the compartments. In such a construction the base of the first compartment comprises a plug connectable part, and the mouth opening of the second compartment comprises a socket connectable part.

For example the dosage form may include one or more linker unit positioned between adjacent pairs of capsule compartments, preferably with at least one weld in the dosage form may be between a capsule compartment and such a linker unit. Such a linker unit may for example have connectable parts which are connectable to the above-mentioned first and/or second connectable parts on the adjacent capsule compartments. Suitably to facilitate a linear assembly of capsule compartments in the dosage form a linker unit may have its connectable parts in opposite linear facing directions. Suitably such a linker unit may comprise a closure for the mouth opening of a capsule compartment, e.g. connecting with the capsule compartment in the manner of a plug or a cap for its mouth opening, and having a connectable part enabling connection to an adjacent sub-unit, e.g. another capsule compartment. If a capsule compartment is made of a sustained release component, then preferably such a linker / closure is also made of a sustained release component, so that the entire capsule compartment envelope of compartment and closure is a sustained release envelope.

In a specific form the linker may have one or two connectable parts which connect with the mouth opening of a capsule compartment. For example such a linker may have two connectable parts which are opposite facing plug parts and which can connect in a plug and socket manner with the mouth opening of two oppositely-facing capsule compartments to thereby form a capsule-linker-capsule assembly. Suitably welds, e.g. ultrasonic welds, may be formed between both of the capsule compartments and the linker between them in such a dosage form.

For example a linker may comprise a closure for the mouth opening of a capsule compartment, and this linker may have one or more first and/or second connectable parts such that the first or second part on the closure may connect with respectively the second or first part on an adjacent capsule compartments in a suitable configuration.

For example in one form such a linker / closure may be provide with two oppositely-facing plug connectable parts which can connect with the mouth openings of opposite-facing capsule compartments. Such a closure can thereby act as a linker between two capsule compartments with their mouth openings oppositely facing, in

a capsule compartment – linker – capsule compartment linear arrangement. For example this arrangement may be an end compartment – linker – end compartment arrangement.

Other ways in which such a linker may be used in a dosage form of the invention will be apparent. For example an intermediate capsule compartment may be in the form of a generally cylindrical shape with two oppositely facing open ends, and two linkers may connect via respectively one each of their connectable parts with an open end of the cylinder, leaving the other connectable part available for connection to respectively another sub-unit.

Preferably at least one, preferably both, of the connectable parts of the linker is a plug part which fits in a plug-and-socket manner into the open end of a capsule compartment. Therefore such a plug part is typically a cylindrical shape, corresponding closely to the internal shape of the open end of a capsule compartment adjacent to the open end.

Preferably the linker is in the form of a solid wall part with oppositely facing plug connectable parts, oppositely facing end surfaces of the plug parts extending generally transverse to the longitudinal direction of the linker. Preferably each plug part is a snug friction fit into the open end of a capsule compartment. Preferably each plug part is provided with an abutment surface to define and limit the extent to which each plug part can extend into the open end of a capsule compartment by abutting against the rim of the open end of a capsule compartment when the plug part extends to a suitable extent into the capsule mouth.

In a preferred construction, the linker comprises a generally cylindrical solid body, its opposite facing ends being plug parts, with two oppositely facing abutment surfaces each being a surface of a ledge formed around the circumference of the cylindrical body and generally planar in a plane perpendicular to the length direction. Such a ledge may typically be ring shaped with its plane perpendicular to the longitudinal direction of the capsule. With such a linker the assembled dosage form may comprise two capsule compartments each in the shape of a cylinder having one open end and one closed end (e.g. the above-described tub or bucket shapes), with their open ends in an opposite facing relationship, with a linker

between them with each of the opposite facing plug parts of the linker fitting in a plug-and-socket manner into the open end of a capsule compartment, with an ultrasonic weld formed between a plug part and/or an abutment surface of the linker and the compartment wall in the vicinity of the open end, e.g. the rim of the open end.

A preferred construction of multicompartment capsule assembly comprises a capsule compartment made of a sustained release component, capsule compartment made of an immediate release component, and a linker between them made of a sustained release component. In such a construction the immediate release compartment may breach and release its content, leaving the envelope of compartment and closure as a sustained release envelope to release its contents in e.g. the intestine.

In the process of injection moulding a fluid polymer is injected under pressure into a precisely made die cavity in a mould block. Injection moulding processes can enable the sub-units to be made with the precision necessary to achieve connection by tight friction-fit or snap-fit interlocking and to maintain suitable contact between adjacent parts to facilitate a weld. Suitable techniques of injection moulding are known from for example the art of manufacture of small plastic components e.g. small parts of LEGO® toys. Processes such as those described in Cuff. G and Raouf. F, *supra*, may be used to manufacture such solid sub-units and capsule compartments via injection moulding.

Consequently the invention also provides for a molding process, for example an injection molding or powder compression process, wherein sub-units, including the solid sub-units and capsule compartments of the dosage form are made in respective mould cavities of the pharmaceutically acceptable polymeric blends.

For purposes herein representative examples of polymers suitable for injection molding into single or multicomponent dosage forms and for use in pharmaceutical applications, include, but are not limited to, poly(ethylene) oxides (PEO), polyethylene glycol's (PEG), mixtures of Peg's and PEO's, polyvinyl alcohol (PVA), polyvinyl acetate, povidone (polyvinyl pyrrolidone), cellulose derivatives such as

carboxymethyl cellulose, methyl cellulose, ethylcellulose, hydroxyethyl cellulose, hydroxypropylcellulose, hydroxyethyl methylcellulose, hydroxypropylmethyl cellulose (HPMC), hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, noncrystalline cellulose, starch and its derivatives such as hydroxyethyl starch, sodium starch glycolate, natural polymers (such as polysaccharides like pullulan, carrageenan, xanthan, chitosan or agar gums), polyacrylates and poly (meth)acrylates, and its derivatives such as the Eudragit family of polymers available from Rohm Pharma, poly(alpha-hydroxy acids) and its copolymers such poly(caprolactone), poly(lactide-co-glycolide), poly(alpha-aminoacids) and its copolymers, polyglycolysed glycerides (such as Gelucire® 44/14, Gelucire® 50/02, Gelucir®e 50/13 and Gelucire® 53/10), carboxyvinyl polymers (such as Carbopols), and polyoxyethylene-polyoxypropylene copolymers (such as Poloxamer 188™); and combinations or mixtures thereof.

Also potentially suitable for use herein are the polymers poly(orthoesters), polyphosphazenes, poly(phosphoesters), and polyanhydrides, and combinations or mixtures thereof may also be suitable for use herein.

Additionally, hyaluronic acid, alginates, carragenen, collagen, gelatin, and albumen may also be suitable for injection molding herein, either alone or in combination with another polymeric blend. It is recognized that the ultimate choice of polymers if not previously approved by the regulatory agencies of the world, are in the category of generally recognized as safe (GRAS) approved. Ultimately, if the polymer does not dissolve to release the contents of the component or sub-unit, the component may contain pore-forming reagents to allow the contents of the gastro-intestinal tract to enter the sub-unit and dissolve the active agent(s) therein. In such a capacity the sub-unit or dosage form will act more as a delivery device, and not as a capsule or controlled release modifying reagent. It is recognized that the choice of polymer will depend upon the desired outcome and the regulatory agency under which approval is being sought.

More suitably, methacrylic acid copolymers (such as Eudragit E®, Eudragit E100® Eudragit® L and/or Eudragit® S), poly(meth)acrylate copolymers, such as Eudragit® 4135F, and ammonium methacrylate copolymers (such as Eudragit® RL and/or Eudragit® RS), are preferred.

Acrylic and/or methacrylic acid-based polymers which are soluble in intestinal fluids and which can be formed into capsules are for example disclosed in US 5,705,189 (Roehm GmbH) the content of which is incorporated herein by reference in its entirety. These poly(meth)acrylate copolymers were extrudable and injection molded into capsule half's wherein the ratio of acrylic and/or methacrylic acid was generally 20% w/w or more off the copolymer (Examples 1-8). In these Examples, glycerol monosterate was added on a 3-5% wt base of the polymer as a mold-releasing agent.

A particular polymer disclosed in US 5,705,189, as emulsion E2 (column 6, line 10) being a copolymer of methacrylic acid, methyl methacrylate and methyl acrylate (suitably in a ratio of 10:25:65) has been found to be a preferred polymer for use in the present invention. This ratio of components is also known as Eudragit ® 4135F, and is a solid product obtained from Eudragit FS 30D. However, it has been found that the unblended polymer alone is not suitable for injection molding, but must be blended in accordance with the teachings herein to produce non-distorted, unwarped capsule/sub-unit components for assembly into either single capsule or multicompartment dosage forms. For the polymer 4135F, at least one lubricant and one dissolution modifying agent is necessary to achieve quality, non-distortion molded components which readily release from the injection molds. The polymers exemplified in US 5,705,189 all have increased viscosities relative to the blended compositions as used in the this invention.

Therefore, one aspect of this invention is the novel blending of excipients to render this polymer suitable for injection molding into capsules and multicompartmental units.

A preferred polymer is a material that preferentially dissolves or disintegrates at different points in the digestive tract. As noted above, such polymers include the known acrylic and/or methacrylic acid-based polymers, which are soluble in intestinal fluids, e.g. the Eudragit™ series of commercially available polymers. Examples of these include Eudragit E™, such as Eudragit E 100™, which preferentially dissolves in the more acid pH of the stomach, or enteric polymers such as Eudragit L™ and/or Eudragit S™ which preferentially dissolve in the more alkaline pH of the intestine.

Other preferred polymers also include polymers which dissolve slowly, e.g. a predetermined rate in the digestive tract, such as Eudragit RL™, e.g. Eudragit RL 100™, and/or Eudragit RS™ e.g. Eudragit R100™, and/or blends of such Eudragit™ polymers. A preferred blend would be the combination of RL and RS with the necessary glidants and excipients.

The polymer Eudragit 4135F™ dissolves only above pH 7, e.g. in the colon and so is suitable for formulation as a sustained release component. In contrast, as noted, the polymer Eudragit E100™ dissolves in acid as so is suitable for use as an immediate release component.

Most of these pharmaceutically acceptable polymers are described in detail in the Handbook of Pharmaceutical excipients, published jointly by the American Pharmaceutical association and the Pharmaceutical society of Britain.

Preferably, the polymeric carriers are divided into three categories: (1) water soluble polymers useful for rapid dissolve and immediate release of active agents, (2) water insoluble polymers useful for controlled release of the active agents; and (3) pH sensitive polymers for pulsatile or targeted release of active agents. It is recognized that combinations of both carriers may be used herein. It is also recognized that

several of the poly(meth)acrylates are pH dependent for the solubility and may fall into both categories.

Water soluble polymers generally include but are not limited to, poly(ethylene oxide), polyvinyl alcohol, polyvinyl pyrrolidone, hyaluronic acid, alginates, carragenen, cellulose derivatives such as carboxymethyl cellulose sodium, hydroxyethyl cellulose, hydroxypropylcellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, starch and its derivatives such as hydroxyethyl starch, sodium starch glycolate, dextrin, chitosan and its derivatives, albumen, zein, gelatin, and collagen.

Preferably, a water-soluble polymer for use herein either as a base polymer material or as a dissolution modifying agent is polyethylene oxide, such as the brand name POLYOX®. It is recognized that the polymers may be used in varying molecular weights, with combinations of molecular weights for one polymer being used, such as 100K, 200K, 300K, 400K, 900K and 2000K. Sentry POLYOX is a water soluble resin, which is listed in the NF and have approximate molecular weights from 100K to 900K and 1000K to 7000K.

Water insoluble polymers generally include but are not limited to, polyvinyl acetate, methyl cellulose, ethylcellulose, noncrystalline cellulose, polyacrylates and its derivatives such as the Eudragit family of polymers available from Rohm Pharma (Germany), poly(alpha-hydroxy acids) and its copolymers such as poly(ε-caprolactone), poly(lactide-co-glycolide), poly(alpha-aminoacids) and its copolymers, poly(orthoesters), polyphosphazenes, poly(phosphoesters), and polyanhydrides.

These pharmaceutically acceptable polymers and their derivatives are commercially available and/or are prepared by techniques known in the art. By derivatives it is meant, polymers of varying molecular weight, modification of functional groups of the polymers, or co-polymers of these agents, or mixtures thereof.

Further, two or more polymers may be used in combination to form blends having the desired characteristics, such as enhanced flow, flexibility in molding or desired drug release profile.

It is recognized that polymeric composition which are first melted in a melt extrusion process, may also contain additional additives or excipients to assists in melt flow, strength, brittleness, and other molding characteristics, these additional excipients include but are not limited to, plasticizers, absorption enhancers, additional surfactants, flavouring agents, dyes, etc.

While the compositions herein may be moulded in varying wall-thickness, it is preferably that capsules or components have a wall-thickness of about 0.3 to about 0.8mm. However, dissolution performance will more appropriately tailor the wall thickness depending upon the release profiles desired. Increases in wall thickness may be necessary to reduce warping of the components, or modification of the additional excipients in addition to this may be necessary.

The polymer material(s) may include other substances to modify their properties and to adapt them to various applications, including but not limited to surfactants, absorption enhancers, lubricants, plasticizers, dissolution modifying agents, processing aids, colouring agents, flavouring agents and sweetening agents.

Incorporation of a surfactant into the formulation may be necessary or desired to lower the viscosity and surface tension of the formulation/blend, however, in higher amounts it may adversely effect the quality of the resulting dosage form. The surfactant selection may be guided by HLB values but is not necessarily a useful criterion. While HLB surfactants have been utilized herein, such as Tween® 80 (HLB=10), Pluronic F68 (HLB =28), and SDS (HLB>40), lower HLB value surfactants, such as Pluronic F92 may also be used.

A surfactant may also be called an oligomeric surface modifier and includes, but is not limited to: Pluronics® (block copolymers of ethylene oxide and propylene oxide), lecithin, Aerosol OT® (sodium dioctyl sulfosuccinate), sodium lauryl sulfate, Polyoxyl 40™ hydrogenated castor oil, polyoxyethylene sorbitan fatty acid esters, i.e., the polysorbates such as Tween®, such as Tween 20, 60 & 80, the sorbitan fatty acid esters, i.e., sorbitan monolaurate, monooleate, monopalmitate, monosterate, etc. such as Span ® or Arlacel®, Emsorb®, Capmul®, or Sorbester®, Triton X-200, polyethylene glycol's, glyceryl monostearate, Vitamin E-TPGS® (d-alpha-tocopheryl polyethylene glycol 1000 succinate), sucrose fatty acid esters, such as sucrose stearate, sucrose oleate, sucrose palmitate, sucrose laurate, and sucrose acetate butyrate, etc.; and combinations and mixtures thereof. Preferred surfactants are Vitamin E-TPGS®, sucrose fatty acid esters, lecithin, and the Pluronic groups. Suitably, the formulation will contain from about 0 to about 10% w/w surfactant(s).

The polymeric carriers or the second oligomeric surface modifiers, if appropriately chosen, may themselves act as absorption enhancers. Suitable absorption enhancers for use herein, include but are not limited to, chitosan, lecithin, lectins, sucrose fatty acid esters such as the ones derived from stearic acid, oleic acid, palmitic acid, lauric acid, and Vitamin E-TPGS, Labrasol™, or Transcutol™; and combinations or mixtures thereof.

Plasticizers are employed to assist in the melting characteristics of the composition. Exemplary of plasticizers that may be employed in this invention are triethyl citrate (TEC), triacetin, tributyl citrate, acetyl triethyl citrate (ATEC), acetyl tributyl citrate (ATBC), dibutyl phthalate, dibutyl sebacate (DBS), diethyl phthalate, vinyl pyrrolidone glycol triacetate, polyethylene glycol, polyoxyethylene sorbitan monolaurate, propylene glycol, or castor oil; and combinations or mixtures thereof. The polymeric material will determine which plasticizer is suitable for use. For instance, triacetin is not preferred for use with E100 or 4135F but may be suitable for use with Eudragit RS or RL, or PVA for instance. Suitably, the plasticizer is

present in an amount of about 0 to about 20% w/w. Preferably, from about 0 about 5% w/w.

Dissolution modifying agents, or substances which assist in release modification, include but are not limited to poly(ethylene) oxide, the cellulosic derivatives, such as ethyl cellulose and cellulose acetate phthalate; hydroxypropyl cellulose, hydroxypropylmethyl cellulose, and other hydroxyalkylcellulose derivatives; lactose, Starch 1500, and the group of agents generally referred to as disintegrants, such as sodium starch glycollate, croscarmellose sodium, and crospovidone (cross-linked polyvinyl pyrrolidone); and combinations or mixtures thereof. Suitably, the dissolution modifying excipients are in the range of about 2.5% to about 30%w/w. Preferably from about 5 to about 20% w/w. A preferred dissolution modifying excipient is POLYOX, Explotab, Starch 1500, lactose or HMPC.

POLYOX can be seen as representative of a group of hydrophilic non-ionic polymers which melt at the extrusion temperature for the polymer blends, such as about 100°C or greater (100- 190°, preferably about 100-140°C). For instance, Polyox N-80 is molten at 100°C. Polyethylene oxide is also referred to herein as a melt-processing aid and helps to reduce sticking of the polymer in the moulds. Therefore it is functioning as an ejection aid, and a lubricant.

Additional regents, generally classified as processing aids, include strengthening agents, such as talc. Suitably, the processing aids are present from about 0 to about 10% w/w.

Suitable mold processing lubricants or glidants for use herein, include but are not limited to, stearyl alcohol, stearic acid, glycerol monosterate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, and fumed silica; and combinations or mixtures thereof. This functions primarily as a flow promoter for the composition. A preferred lubricant is stearyl alcohol, or GMS. A commercial grade of stearyl alcohol, such as Crodacol S95 (Croda Oleochemicals) is preferred

for use herein. The material should be suitable for milling. A combination of POLYOX and stearyl alcohol has also been found effective for use with the polymer Eudragit E100. Suitably, the amount of lubricant present in the formulation is from about 0 to about 30% w/w, preferably from about 10 to about 25% w/w.

Stearyl alcohol has the advantage that it acts as a mould processing lubricant but causes no mould distortion, i.e. crumpling of the multidosage compartment shell when the hot soft shell is taken out of the mould, which might result from a lubricant which made the blend flow better. An another alternate material also useable as lubricant/flow promoters is lecithin (a natural product). Suitably, the lubricants for use herein do not introduce any metal ion contamination.

The final products of this invention, i.e. the capsules, and or components or sub-units may additionally include materials in the polymer materials of which they are made to enhance the ease with which they can be welded together. The sub-units may additionally be provided with constructional features and/or include materials in the polymer materials of which they are made to enhance the ease with which they can be welded together, e.g. opacifier materials such as carbon (e.g. 0.2-0.5%), iron oxides or titanium dioxide (e.g. 0.5-1.0%) to help the polymer to absorb laser energy. Such opacifier materials are generally regarded as safe.

For example each of a plurality of sub units, e.g. of the capsule compartments, solid sub-units, or combinations thereof may comprise the same or different polymer(s). For example each of a plurality of sub units, e.g. of capsule compartments, solid sub-units, or combinations thereof may comprise the same or different drug substance. For example each sub-unit may contain the same drug substance but release the contents into the gastro-intestinal tract of the patient at a different rate, at different times after administration to the patient or at different places in the patient's gastro-intestinal system. Alternatively each sub-unit may contain a different drug substance, each of which may be released at the same or a different rate or time after administration or place in the patient's gastro-intestinal system.

For example two or more sub-units, e.g. two capsule compartments, may each contain different drug substances, and/or different drug substance formulations, and/or the same drug in different formulations, so that a combination of two or more drug substances or formulations may be administered to a patient.

The dosage form of this invention enables the assembly together of sub-units which differ in their drug content and/or drug content release characteristics to provide a dosage form tailored to specific administration requirements.

The dimensions and shape of each of the sub-units and hence of the overall assembled dosage form may be determined by the nature and quantity of the material to be contained therein and the intended mode of administration and intended recipients. For example a dosage form intended for oral administration may be of a shape and size similar to that of known capsules intended for oral administration.

The dosage form is particularly suitable for presentation as an oral dosage form containing one or more drug substances suitable for oral administration, and appears to be suitable for all types of such drug substance.

The drug substance(s) contained in any capsule compartment may be present in any suitable form, e.g. as a powder, granules, compact, microcapsules, gel, syrup or liquid provided that the capsule compartment wall material is sufficiently inert to the liquid content of the latter three forms. The contents of the compartments, e.g. drug substances, may be introduced into the compartments by standard methods such as those used conventionally for filling capsules, such as dosating pins or die filling.

The sub-units may differ from each other in their drug content release characteristics, and this may be achieved in various ways. For example one or more solid sub-units and/or capsule compartments may be substantially immediate release, i.e. releasing their drug contents substantially immediately upon ingestion or on

reaching the stomach. This may for example be achieved by means of the matrix polymer or the capsule compartment wall dissolving, disintegrating or otherwise being breached to release the drug content substantially immediately. Generally, immediate-release sub-units are preferably provided by being capsule compartments.

For example one or more solid sub-units and/or capsule compartments may be sustained-release sub-units. Preferably these are solid sub-units, as a bulk matrix of polymer is likely to dissolve or disperse more slowly to release its drug content that a thin walled capsule.

For example one or more solid sub-units and/or capsule compartments may be pulsed-release sub-units for example releasing their drug content at a specific predetermined point in a patient's gastro-intestinal system. This may be achieved by the use of polymer materials which dissolve or disperse only at defined pH environments, such as the above mentioned Eudragit® polymers. For instance, E100 is acid labile.

For example in the above-described capsule compartment-linker-capsule compartment dosage form one capsule compartment may be effectively immediate release and the other may be sustained, delayed or pulsed release. To achieve this for example one capsule compartment may be made of polymer materials which cause the capsule compartment to release its drug content in the stomach or upper part of the digestive tract, and the linker (acting as a closure for the second compartment) and the second compartment itself may be made of materials e.g. the above described enteric polymers, which release their drug content only in the intestinal environment.

Determination of the time or location within the gastro-intestinal tract at which a sub-unit releases its drug substance content may be achieved by for example the nature of the sub-unit material, e.g. a solid sub-unit matrix polymer or a capsule compartment wall material, or in the case of an end compartment which is closed by

a closure, by the nature of the closure material. For example the wall of different, e.g. adjacent, compartments may be made of polymers which are different or which otherwise differ in their dissolution or disintegration characteristics so as to endow different compartments with different drug release characteristics. Similarly for example the polymer matrix material of different, e.g. adjacent, solid sub-units may be made of polymers which are different or which otherwise differ in their dissolution or disintegration characteristics so as to endow different solid sub-units with different drug release characteristics.

For example the matrix, wall or closure material may be a polymer which dissolves or disperses at stomach pH to release the drug substance in the stomach. Alternatively the wall material of different compartments may differ so that different compartments have different release characteristics.

For example a solid sub-unit or a capsule compartment may have respectively a matrix or a wall or a closure comprising an enteric polymer which dissolves or disperses at the pH of the small or large intestine to release the drug substance in the intestine. Suitable such polymers have been described above, for example with reference to US 5,705,189.

Additionally or alternatively the wall material may differ in thickness between compartments so that thicker walled compartments disrupt more slowly than thinner walled compartments.

Additionally or alternatively the compartment walls or the closure may have areas or points of weakness which preferentially dissolve and may thereby determine the time of onset and/or rate of release of the drug substance content. For example such points of weakness may comprise holes, e.g. small holes, e.g. laser-drilled holes in the compartment wall or the closure, these holes being closed and/or covered with a film of a polymer material that dissolves at a pre-determined point in the digestive tract, for example an enteric polymer material. For example such points of weakness

may comprise thinned parts in a capsule compartment wall formed during the moulding operation in which the capsule compartment is formed.

The sub-units may additionally or alternatively have surface or other constructional features that modify their drug release characteristics. For example solid sub-units may be provided with internal cavities or channels to create a large surface area. For example solid sub-units may be in the form of hollow cylinders, donuts, or toroids, which shapes are known to tend towards first-order dissolution or erosion in liquid media and correspondingly to tend toward first-order release of drug content dispersed therein.

Pharmaceutically acceptable agents, actives or drugs as used herein, is meant to include active agents having a pharmacological activity for use in a mammal, preferably a human. The pharmacological activity may be prophylactic or for treatment of a disease state.

As used herein the term's "active agent", "drug moiety" or "drug" are used interchangeably.

Water solubility of an active agent is defined by the United States Pharmacoepia. Therefore, active agents which meet the criteria of very soluble, freely soluble, soluble and sparingly soluble as defined therein are encompassed this invention.

Suitable drug substances can be selected from a variety of known classes of drugs including, for example, analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics (including penicillin's), anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobactefial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytic sedatives (hypnotics and neuroleptics), astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, corticosteroids, cough

suppressants (expectorants and mucolytics), diagnostic agents, diuretics, dopaminergics (antiparkinsonian agents), haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radiopharmaceuticals, sex hormones (including steroids), anti-allergic agents, stimulants and anorexics, sympathomimetics, thyroid agents, PDE IV inhibitors, NK3 inhibitors, CSBP/RK/p38 inhibitors, antipsychotics, vasodilators and xanthines.

Preferred drug substances include those intended for oral administration and intravenous administration. A description of these classes of drugs and a listing of species within each class can be found in Martindale, The Extra Pharmacopoeia, Twenty-ninth Edition, The Pharmaceutical Press, London, 1989, the disclosure of which is hereby incorporated herein by reference in its entirety. The drug substances are commercially available and/or can be prepared by techniques known in the art.

The polymeric blends can be preferably selected from known pharmaceutical polymers. The physico-chemical characteristics of these polymers, as well as the thickness of the ultimate injection molded component, will dictate the design of the dosage form, such as rapid dissolve, immediate release, delayed release, modified release such as sustained release, controlled release, or pulsatile release etc.

The polymer blends are made by well-known methods for producing hot melt extrusions in which the selected ingredients are fed into a feed hopper of an extrusion machine. Suitable well known equipment is readily available for producing a hot melt extrusion of the blends herein.

Immediate Release Capsules or Components

While suitable polymers are taught herein, the commercially available Eudragit E100 (Rohm) is a preferred polymer for immediate release characteristics. To make this polymer extrudable into the thin walled component shells (such as a 0.5 mm wall thickness) E100 may be blended with several excipients as described herein.

Preferably, Eudragit E100 is blended with dissolution modifying agents such as POLYOX. Preferred lubricating agents are stearyl alcohol.

Eudragit E 100 is also referred to as butylmethacylat-(2-dimethylaminoethyl)-methacrylat-methylmethacylat-copolymer (1:2:1), is a copolymer based on (2-dimethylaminoethyl)methacryalate, butyl methacrylate and methyl methacrylate having a mean molecular weight of about 150,000. It contains not less than 20.8 and not more than 25.5 % dimethylaminoethyl groups in the dry substance. Eudragit is produced by Rohm Pharma, Germany.

Slow/delayed Release Capsules or Components

For production of a slow release, or a delayed release capsule or component in a multidosage capsule, the polymer Eudragit 4135F (Röhm), is preferred. The principal problem with Eudragit® 4135F in its unformulated state is its high dissolution time, in excess of 30 hours in aqueous media e.g. in SIF (simulated intestinal fluid). Therefore, to improve its dissolution time the polymer is blended with one or more hydrophilic excipients. This will enhance the absorption of water by the Eudragit 4135F polymer, and so accelerate the rate at which the blended polymer swells on absorption of water.

A preferred multicomponent dosage form is that disclosed in PCT/EP00/07295, filed as Attorney Docket No. P32374 on July 27, 2000 and incorporated by reference herein in its entirety. The multicomponent dosage form of this application preferably uses an ultrasonic weld to seal to components together. The Eudragit 4135F will open to release its contents by swelling in the region of the ultrasonic weld, which causes separation at the weld.

A number of hydrophilic excipients may be used such as the known disintegrants represented by "Explotab", "Kollidon-CL", (cross-linked PVP), swelling agents such as polyvinyl pyrrolidone, cellulosic derivatives such as hydroxypropyl methyl cellulose (HPMC), wicking agents such as low molecular weight solutes, e.g.

manitol, lactose, and starch; inorganic salts such as sodium chloride (typically at 5-10%). While PEG (polyethylene glycol) may also be acceptable, in combination with the 4135F it was found to act too much like a lubricant and resulted in mould distortion of the hot moulded shells when they are taken out of the mould. Gelucire (a fatty acid PEG ester) may cause a similar problem, due to traces of PEG in the Gelucire. Preferably, the hydrophilic excipient is one which does not melt at the extrusion temperature, e.g. the lactose, inorganic salts, and HPMC, such as Pharmacoat 603 (an HPMC with a glass transition temperature 175°C). Additionally, as a lubricant, stearyl alcohol is preferred. For the same reasons as with the E100 immediate release component it has been found to enhance flow, i.e. and is used preferably at the same proportion (2.5 – 15%) as with E100. It is also found that higher proportions of stearyl alcohol increase the flowability so as to enable molding of thinner walls.

Spacer Components

This is the plug like linker that closes and connects the two end compartments of the capsules (such as immediate release and slow/sustained release compartments). This can be made of the same polymer blend (4135F blend) as the slow/delayed release component, but can equally well be made of 4135F blended with a suitable lubricant, such as stearyl alcohol, but without other hydrophilic excipients. By not including the hydrophilic excipient in the spacer the opening of the slow/delayed release component will be improved because of the mismatch in water disturbance and thus differential swelling, of the slow/delayed release component and the spacer acting as a plug closure of the compartment.

Preferably, use of a delayed release polymer to form a slow/delayed release component or sub-unit which is part of a multicomponent dosage form, will provide for a means to release the contents of the sub-unit by failure of the weld, as the thin region of the end cap compartments which overlap the linker plug swells rapidly and will pull away from the adjacent spacer, thereby opening the contents of the sub-unit into the gastrointestinal fluids.

EXAMPLES

The invention will now be described by reference to the following examples, which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. All temperatures are given in degrees centigrade; all solvents are highest available purity unless otherwise indicated.

Example 1

Manufacture of multicomponent pharmaceutical dosage forms with pharmaceutically acceptable polymeric compositions as described herein. Example 1 will describe a general process used to mold the various multicomponent capsules and appropriate subunits. Additional pharmaceutical compositions are shown and described below.

Item number	Material	% w/w
1.	Copolymer of methacrylic acid, methyl acrylate and methylmethacrylate (Eudragit 4135)	73.0
2.	Hydroxypropyl Methylcellulose (Pharmacoat 603)	10.0
3.	Lactose monohydrate	5.0
4.	Stearyl alcohol, milled	12.0
	Total	100

Using a suitable blender mix together:

Item 2. Hydroxypropyl Methylcellulose (Pharmacoat 603)

Item 3. Lactose monohydrate

Item 4. Stearyl alcohol, milled

to form a homogeneous powder blend.

Set up a suitable co-rotating twin screw hot melt extruder with both a pellet feeder and a powder feeder together with strand cooling equipment and a pelletizer. Fit the selected mould in the injection molding machine. Example processing parameters are as follows:

Extruder:	
Screw speed	300 rpm (range 100 – 500 rpm)
Temperature of zone 1 (feed zone)	60°C (range 30 - 75°C)
Temperature of zone 2	115°C (range 85 - 130°C)
Temperature of zone 3	120°C (range 90 - 135°C)
Temperature of zone 4	125°C (range 95 - 140°C)
Temperature of zone 5	130°C (range 100 - 145°C)
Temperature of strand die	135°C (range 105 - 150°C)
Pellet feeder	1 .6 kg/hour (0.7 - 2.1 kg/hour)
Powder feeder	0.6 kg/hour (0.26 - 0.79 kg/hour)
Strand cooling equipment:	Appropriate for extrusion rate used
Pelletiser:	Appropriate for extrusion rate used
Injection moulder:	Appropriate injection/cooling times, temperature and injection pressure, dependent on machine type and pellet formulation.

Pre-heat the extruder to the appropriate temperature. Load the pellet feeder with the Copolymer of methacrylic acid, methyl acrylate and methylmethacrylate (Eudragit 4135F) and the powder feeder with the blend. Start the extruder screws rotating and then start the two feeders. Process the extruded strand along the cooling equipment into the pelletiser and collect the pellets formed.

Input appropriate machine settings and pre-heat the injection moulder. Load the hopper with the pellets and mold the multi-components units.

Additional examples or embodiments of this example, using the same process steps but with variant formulations are as shown below:

Example #	Formulation (%w/w)	
Example 2	Eudragit 4135F	75.0
	Stearyl alcohol	5.0
	Ac-Di-Sol (croscarmellose sodium)	20.0
Example 3	Eudragit 4135F	75.0
	Stearyl alcohol	5.0
	Explotab (sodium starch glycollate)	20.0
Example 4	Eudragit 4135F	85.0
	Stearyl alcohol	5.0
	Xylitol	10.0
Example 5	Eudragit 4135F	75.0
	Stearyl alcohol	5.0
	Ac-Di-Sol (crocarmellose sodium)	10.0
	Xylitol	10.0
Example 6	Eudragit E100	75.0
	Stearyl alcohol	5.0
	PolyOx WSR N-80	20.0

Example #	Formulation (%w/w)	
Example 7	Eudragit 4135F	75.0
	Stearyl alcohol	5.0
	Mannitol	10.0
	Explotab (sodium starch glycollate)	10.0
Example 8	Eudragit 4135F	65.0
	Stearyl alcohol	5.0
	Mannitol	10.0
	Explotab (sodium starch glycollate)	20.0
Example 9	Eudragit 4135F	80.0
	Stearyl alcohol	5.0
	Explotab (sodium starch glycollate)	10.0
	Lactose monohydrate	5.0
Example 10	Eudragit 4135F	75.0
	Stearyl alcohol	5.0
	Explotab (sodium starch glycollate)	10.0
	Lactose monohydrate	10.0
Example 11	Eudragit 4135F	85.0
	Stearyl alcohol	5.0
	Lactose monohydrate	10.0
Example 12	Eudragit 4135F	75.0
	Stearyl alcohol	5.0
	Lactose monohydrate	20.0
Example 13	Eudragit 4135F	80.0
	Stearyl alcohol	5.0
	Explotab (sodium starch glycollate)	5.0
	Lactose monohydrate	10.0
Example 14	Eudragit 4135F	70.0
	Stearyl alcohol	5.0
	Explotab (sodium starch glycollate)	5.0

	Lactose monohydrate	20.0
Example 15	Eudragit 4135F	75.0
	Stearyl alcohol	10.0
	Mannitol	7.5
	Explotab (sodium starch glycollate)	7.5

Example #	Formulation (%w/w)	
Example 16	Eudragit 4135F	80.0
	Stearyl alcohol	5.0
	Starch 1500	10.0
Example 17	Eudragit 4135F	85.0
	Stearyl alcohol	5.0
	Starch 1500	15.0
Example 18	Eudragit 4135F	80.0
	Stearyl alcohol	5.0
	Starch 1500	10.0
	Lactose monohydrate	5.0
Example 19	Eudragit 4135F	85.0
	Stearyl alcohol	5.0
	Kollidon CL	10.0
Example 20	Eudragit 4135F	80.0
	Stearyl alcohol	5.0
	Explotab (sodium starch glycollate)	10.0
	Lactose monohydrate	5.0
Example 21	Eudragit 4135F	75.0
	Stearyl alcohol	10.0
	Explotab (sodium starch glycollate)	10.0
	Lactose monohydrate	5.0
Example 22	Eudragit 4135F	85.0
	Stearyl alcohol	5.0
	Sodium chloride	5.0
	Lactose monohydrate	5.0
Example 23	Eudragit 4135F	85.0
	Stearyl alcohol	5.0
	Klucel LF	5.0
	Lactose monohydrate	5.0

Example 24	Eudragit 4135F	85.0
	Stearyl alcohol	5.0
	Pharmacoat 603	5.0
	Lactose monohydrate	5.0

Example #	Formulation (%w/w)	
Example 25	Eudragit 4135F	80.0
	Stearyl alcohol	10.0
	Pharmacoat 603	5.0
	Lactose monohydrate	5.0
Example 26	Eudragit 4135F	80.0
	Stearyl alcohol	10.0
	Explotab (sodium starch glycollate)	5.0
	Lactose monohydrate	5.0
Example 27	Eudragit 4135F	80.0
	Stearyl alcohol	10.0
	Hypromellose phthallate	5.0
	Lactose monohydrate	5.0
Example 28	Eudragit 4135F	80.0
	Stearyl alcohol	10.0
	Low substituted hydroxypropylcellulose	5.0
	Lactose monohydrate	5.0
Example 29	Eudragit 4135F	90.0
	Stearyl alcohol	5.0
	Pharmacoat 603	5.0
Example 30	Eudragit 4135F	90.0
	Stearyl alcohol	5.0
	Lactose monohydrate	5.0

Dissolution time in the simulated intestinal fluid, at a pH of 7. 5 for 100% release was determined for a number of the Examples illustrated above. The results are summarized in the table below.

Formulation	Dissolution time in SIF, pH 7.5 for 100% release
Example 17	9 - 16hrs
Example 18	11 - 18hrs
Example 19	3 - 11hrs
Example 20	4 - 13hrs
Example 22	5 - 18hrs
Example 29	2 - 9hrs
Example 30	6 - 12hrs
Example 11	5 - 11hrs
Example 12	6 - 14hrs

Example 13

In accordance with the process described above in Example 1 for the manufacture of pellets, actual (averaged) processing parameters for the following material composition used were:

Material	%w/w
Eudragit 4135F	75.0
Sodium starch glycollate (Explotab)	20.0
Stearyl alcohol	5.0

Extruder: PRISM 24 mm twin screw.

Extrusion conditions (mean):

Extruder screw speed (rpm)	100
Extruder torque (%)	52
Extruder pressure (Bar)	28
Feed rate (kg/hour)	2
Temperature zone 1 (°C)	19
Temperature zone 2 (°C)	120
Temperature zone 3 (°C)	120
Temperature zone 4 (°C)	120
Temperature zone 5 (°C)	120
Temperature zone 6 (°C)	120
Temperature die zone (°C)	130.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the area can, using the preceding description, utilize the present invention to its fullest extent. Therefore, the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is Claimed Is:

1. A pharmaceutical composition for moulded capsules comprising Eudragit 4135F present in an amount of about 50 to 90% w/w; a lubricant present in an amount of 0 to about 30% w/w; a dissolution modifying excipient present in an amount of about 2.5 to about 30% w/w, and optionally a plasticizer present in an amount of 0 to 10% w/w and/or a processing agent present in an amount of 0 to about 10% w/w.

2. The composition according to Claim 1 wherein the lubricant is stearyl alcohol, glycerol monosterate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, or fumed silica; and combinations or mixtures thereof.

3. The composition according to Claim 2 wherein the lubricant is stearyl alcohol.

4. The composition according to any one of Claims 1 to 3 wherein the dissolution modifying excipient is poly(ethylene) oxide, stearic acid, glycerol monosterate (GMS), ethyl cellulose, cellulose acetate phthalate; hydroxypropyl cellulose, hydroxypropylmethyl cellulose, and other hydroxyalkylcellulose derivatives; lactose, Starch 1500, sodium starch glycollate, croscarmellose sodium, or crospovidone (cross-linked polyvinyl pyrrolidone); and combinations or mixtures thereof.

5. The composition according to Claim 1 wherein the plasticizer is triethyl citrate (TEC), tributyl citrate, acetyl triethyl citrate (ATEC), acetyl tributyl citrate (ATBC), dibutyl phthalate, dibutyl sebacate (DBS), diethyl phthalate, vinyl pyrrolidone glycol triacetate, polyethylene glycol, polyoxyethylene sorbitan monolaurate, propylene glycol, or castor oil; and combinations or mixtures thereof.

6. The composition according to Claim 1 wherein the processing agent is talc, lactose, or mannitol.

7. The composition according to Claim 1 wherein the lubricant is present in an amount of 0 to 30% w/w.

8. The composition according to Claim 1 wherein the dissolution modifying excipient is present in an amount of about 5 to about 20% w/w.

9. The composition according to Claim 1 wherein the processing agent is present in an amount of about 1 to about 5 % w/w.

10. The composition according to Claim 1 which further comprises a surfactant.

11. The composition according to Claim 10 wherein the surfactant is a block copolymers of ethylene oxide and propylene oxide, lecithin, sodium dioctyl sulfosuccinate, sodium lauryl sulfate, Polyoxyl 40™ hydrogenated castor oil, polyoxyethylene sorbitan fatty acid esters, the sorbitan fatty acid esters, polyethylene glycol, Vitamin E-TPGS® (d-alpha-tocopheryl polyethylene glycol 1000 succinate), sucrose fatty acid ester; and combinations and mixtures thereof.

12. The composition according to Claim 1 which further comprises an absorption enhancer.

13. The composition according to Claim 12 wherein the absorption enhancer is chitosan, lecithin, lectin, a sucrose fatty acid ester, Vitamin E-TPGS, Labrasol™, or Transcutol™; and combinations or mixtures thereof.

14. The composition according to Claim 1 wherein the Eudragit 4135F is present in an amount of about 50 to 90% w/w.

15. The composition according to Claim 1 or 14 wherein the lubricant is stearyl alcohol, and the dissolution modifying agent is hydroxypropylmethylcellulose, or hydroxypropylcellulose.

16. The composition according to Claim 1 or 14 wherein the lubricant is stearyl alcohol, and the dissolution modifying agent is sodium starch glycollate.

17. The composition according to Claim 15 or 16 wherein the processing aid is mannitol or lactose.

18. The composition according to Claim 1 which is:

Formulation (%w/w)	
Eudragit 4135F	75.0
Stearyl alcohol	5.0
Ac-Di-Sol (croscarmellose sodium)	20.0
Eudragit 4135F	75.0
Stearyl alcohol	5.0
Explotab (sodium starch glycollate)	20.0
Eudragit 4135F	85.0
Stearyl alcohol	5.0
Xylitol	10.0
Eudragit 4135F	75.0
Stearyl alcohol	5.0
Ac-Di-Sol (croscarmellose sodium)	10.0
Xylitol	10.0
Eudragit 4135F	75.0
Stearyl alcohol	5.0
Mannitol	10.0

Explotab (sodium starch glycollate)	10.0
Eudragit 4135F	65.0
Stearyl alcohol	5.0
Mannitol	10.0
Explotab (sodium starch glycollate)	20.0
Eudragit 4135F	80.0
Stearyl alcohol	5.0
Explotab (sodium starch glycollate)	10.0
Lactose monohydrate	5.0
Eudragit 4135F	75.0
Stearyl alcohol	5.0
Explotab (sodium starch glycollate)	10.0
Lactose monohydrate	10.0

Formulation (%w/w)	
Eudragit 4135F	85.0
Stearyl alcohol	5.0
Lactose monohydrate	10.0
Eudragit 4135F	75.0
Stearyl alcohol	5.0
Lactose monohydrate	20.0
Eudragit 4135F	80.0
Stearyl alcohol	5.0
Explotab (sodium starch glycollate)	5.0
Lactose monohydrate	10.0
Eudragit 4135F	70.0
Stearyl alcohol	5.0
Explotab (sodium starch glycollate)	5.0
Lactose monohydrate	20.0
Eudragit 4135F	75.0
Stearyl alcohol	10.0
Mannitol	7.5
Explotab (sodium starch glycollate)	7.5
Eudragit 4135F	80.0
Stearyl alcohol	5.0
Starch 1500	10.0
Eudragit 4135F	85.0
Stearyl alcohol	5.0
Starch 1500	15.0
Eudragit 4135F	80.0
Stearyl alcohol	5.0
Starch 1500	10.0
Lactose monohydrate	5.0
Eudragit 4135F	85.0

Stearyl alcohol	5.0
Kollidon CL	10.0
Eudragit 4135F	80.0
Stearyl alcohol	5.0
Explotab (sodium starch glycollate)	10.0
Lactose monohydrate	5.0

Formulation (%w/w)	
Eudragit 4135F	75.0
Stearyl alcohol	10.0
Explotab (sodium starch glycollate)	10.0
Lactose monohydrate	5.0
Eudragit 4135F	85.0
Stearyl alcohol	5.0
Sodium chloride	5.0
Lactose monohydrate	5.0
Eudragit 4135F	85.0
Stearyl alcohol	5.0
Klucel LF	5.0
Lactose monohydrate	5.0
Eudragit 4135F	85.0
Stearyl alcohol	5.0
Pharmacoat 603	5.0
Lactose monohydrate	5.0
Eudragit 4135F	80.0
Stearyl alcohol	10.0
Pharmacoat 603	5.0
Lactose monohydrate	5.0
Eudragit 4135F	80.0
Stearyl alcohol	10.0
Explotab (sodium starch glycollate)	5.0
Lactose monohydrate	5.0
Eudragit 4135F	80.0
Stearyl alcohol	10.0
Hypromellose phthallate	5.0
Lactose monohydrate	5.0
Eudragit 4135F	80.0

Stearyl alcohol	10.0
Low substituted hydroxypropylcellulose	5.0
Lactose monohydrate	5.0
Eudragit 4135F	90.0
Stearyl alcohol	5.0
Pharmacoat 603	5.0

Formulation (%w/w)		
Eudragit 4135F	90.0	
Stearyl alcohol		5.0
Lactose monohydrate	5.0	

19. An injection moulded capsule shell, linker or spacer having a composition as defined in any one of Claims 1 to 18.

20. A multicomponent injection moulded capsule shell, linker or spacer having a composition as defined in any one of Claims 1 to 18.

21. A welded multicomponent injection moulded capsule shell, linker or spacer having a composition as defined in any one of Claims 1 to 18.

22. A pharmaceutical composition for moulded capsules comprising Eudragit E100, a lubricant, and optionally a dissolution modifying excipient, a plasticizer and/or a processing agent.

23. The composition according to Claim 22 wherein the lubricant is the lubricant is stearyl alcohol, glycerol monosterate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, or fumed silica; and combinations or mixtures thereof.

24. The composition according to Claim 22 wherein the lubricant is the lubricant is stearyl alcohol.

25. The composition according to Claim 22 wherein the dissolution modifying excipient is poly(ethylene) oxide, stearic acid, glycerol monosterate (GMS), ethyl cellulose, cellulose acetate phthalate; hydroxypropyl cellulose, hydroxypropylmethyl cellulose, and other hydroxyalkylcellulose derivatives; lactose, Starch 1500, sodium starch glycollate, croscarmellose sodium, or crospovidone (cross-linked polyvinyl pyrrolidone); and combinations or mixtures thereof.

26. The composition according to Claim 22 or 25 wherein the dissolution modifying excipient is polyethylene oxide.

27. The composition according to Claim 22 wherein the plasticizer is triethyl citrate (TEC), tributyl citrate, acetyl triethyl citrate (ATEC), acetyl tributyl citrate (ATBC), dibutyl phthalate, dibutyl sebacate (DBS), diethyl phthalate, vinyl pyrrolidone glycol triacetate, polyethylene glycol, polyoxyethylene sorbitan monolaurate, propylene glycol, or castor oil; and combinations or mixtures thereof.

28. The composition according to Claim 22 wherein the processing agent is talc, lactose, or mannitol.

29. The composition according to Claim 1 wherein the lubricant is present in an amount of 0 to 30% w/w.

30. The composition according to Claim 22 wherein the lubricant is present in an amount of 10 to 25% w/w.

31. The composition according to Claim 22 or 25 wherein the dissolution modifying excipient is present in an amount of about 2.5 to about 30% w/w.

32. The composition according to Claim 22 or 25 wherein the dissolution modifying excipient is present in an amount of about 5 to about 20% w/w.

33. The composition according to Claim 22 or 28 wherein the processing agent is present in an amount of 0 about 10% w/w.

34. The composition according to Claim 22 wherein the Eudragit E100 is present in an amount of about 50 to 90% w/w.

35. The composition according to Claim 22 wherein the lubricant is stearyl alcohol, and the dissolution modifying agent is hydroxypropylmethylcellulose or hydroxypropyl cellulose.

36. The composition according to Claim 22 wherein the lubricant is stearyl alcohol, and the dissolution modifying agent is glycerol monosterate.

37. The composition according to Claim 22 wherein the dissolution modifying agent is polyethylene oxide.

38. The composition according to Claim 22 which is:

Eudragit E100	75.0
Stearyl alcohol	5.0
Polyethylene oxide	20.0

39. An injection moulded capsule shell, linker or spacer having a composition as defined in any one of Claims 22 to 38.

40. A multicomponent injection moulded capsule shell, linker or spacer having a composition as defined in any one of Claims 22 to 38.

41. A welded multicomponent injection moulded capsule shell, linker or spacer having a composition as defined in any one of Claims 22 to 38.

42. A multi-component pharmaceutical dosage form which comprises a plurality of drug substance – containing sub-units each selected from capsule compartments which can release their drug substance in the gastro-intestinal environment, and solid sub-units comprising a solid matrix of a polymeric composition as defined in Claim 1 or 22, which contains a drug substance, the polymer being soluble, dispersible or disintegrable in the patient's gastro-intestinal environment to thereby release the drug substance, the sub-units being connected together in the assembled dosage form and being retained together by the connection at least prior to administration to a patient, wherein the connection is provided by a weld between parts of the assembled dosage form.

43. A dosage form according to Claim 42 characterised by common interchangeable interconnectable parts so that the sub-units may be assembled in various combinations using the same basic units of capsule compartments, solid sub-units or of solid sub-units and capsule compartments.

44. A dosage form according to Claim 42 or 43 characterised in that the dosage form comprises a plurality of capsule compartments each bounded and physically separated from at least one adjacent compartment by a wall made of a pharmaceutically acceptable polymer material as defined in Claim 1 or 22, adjacent compartments being connected together in the assembled dosage form and being retained together by the connection at least prior to administration to a patient, one or more of the compartments containing a

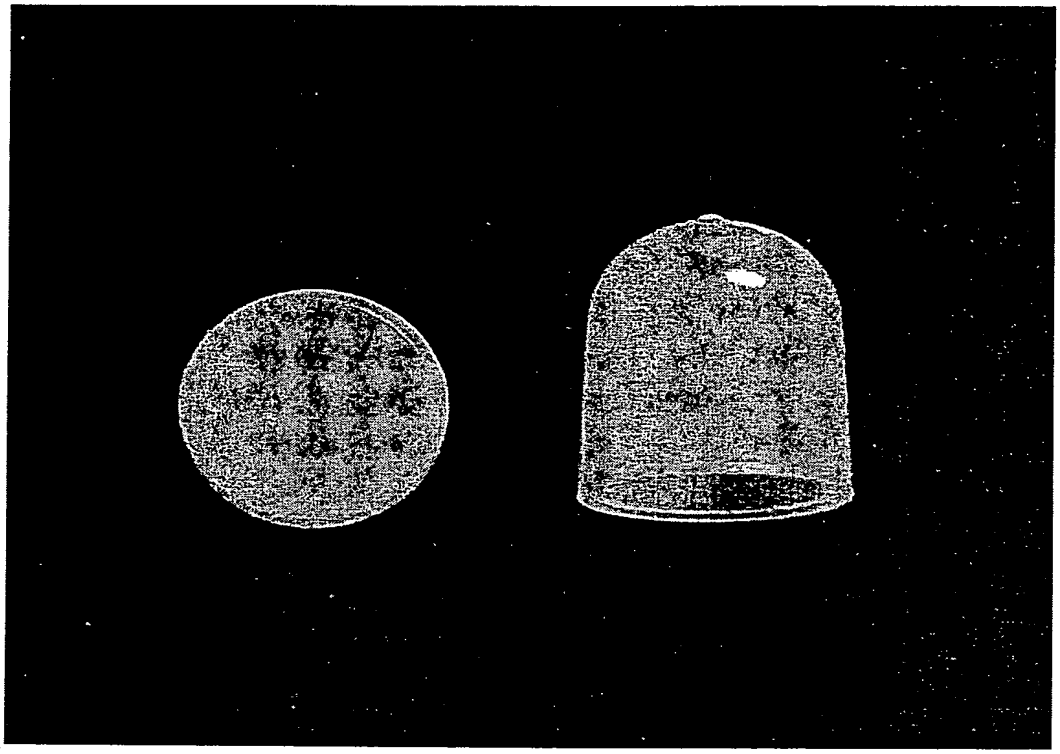
drug substance, and wherein the connection is provided by a weld between parts of the assembled dosage form.

45. A dosage form according to claim 44 characterised in that the wall of the capsule compartment is preferably ca. 0.3 – 0.8 mm, thick.

46. A dosage form according to any one of claims 39 to 45 characterised in that one or more solid sub-units and/or capsule compartments are substantially immediate release.

47. A dosage form according to 19 to 21 or 42 to 45 characterised in that one or more solid sub-units and/or capsule compartments are sustained release or pulsed release

Figure 1



5

Figure 2

5

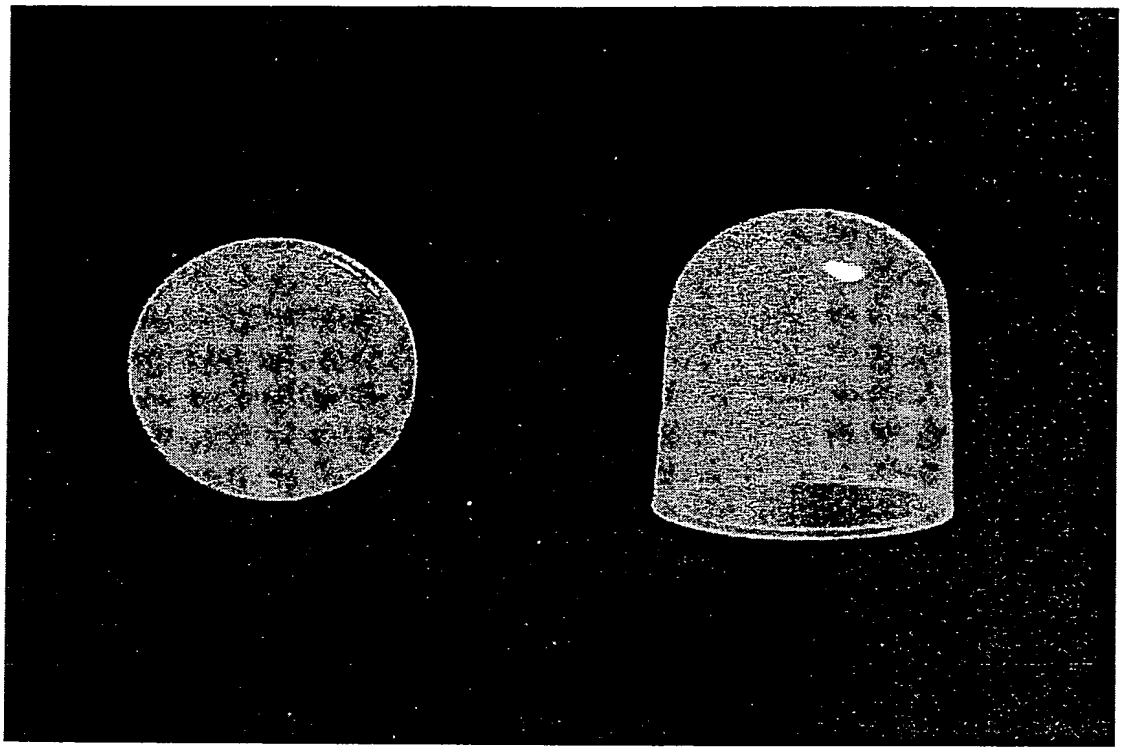


Figure 3

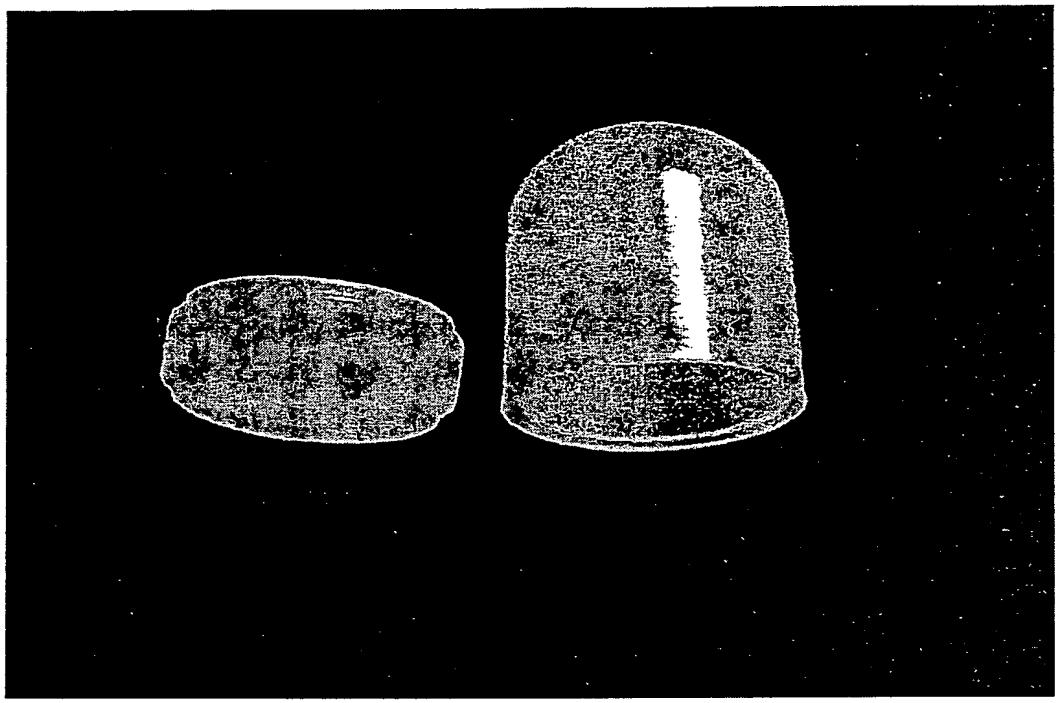


Figure 4

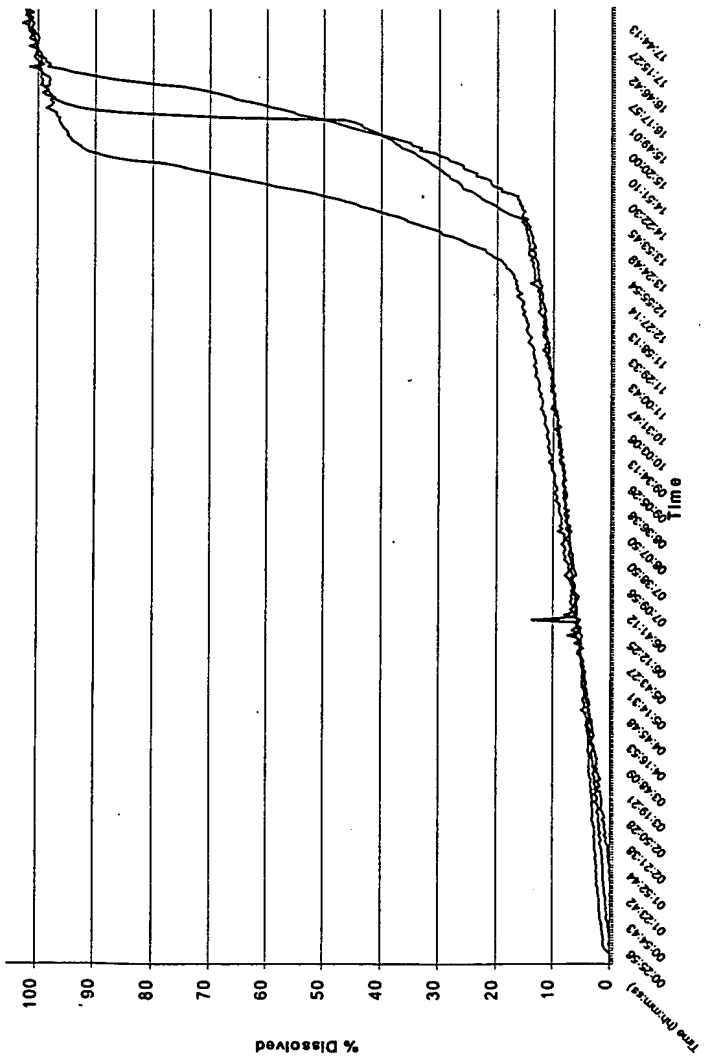

% Dissolved
100
90
80
70
60
50
40
30
20
10
0
Time (hh:mm:ss)
00:25:56
00:54:43
01:23:42
01:52:44
02:21:58
02:50:28
03:19:31
03:48:09
04:16:53
04:45:48
05:14:31
05:43:27
06:12:25
06:41:12
07:09:56
07:38:50
08:07:50
08:36:48
09:05:28
09:34:13
10:03:06
10:31:47
11:00:43
11:29:33
11:58:13
12:27:14
12:55:54
13:24:48
13:53:45
14:22:30
14:51:10
15:20:00
15:48:01
16:17:37
16:46:42
17:15:27
17:44:13
Time

FIGURE 5

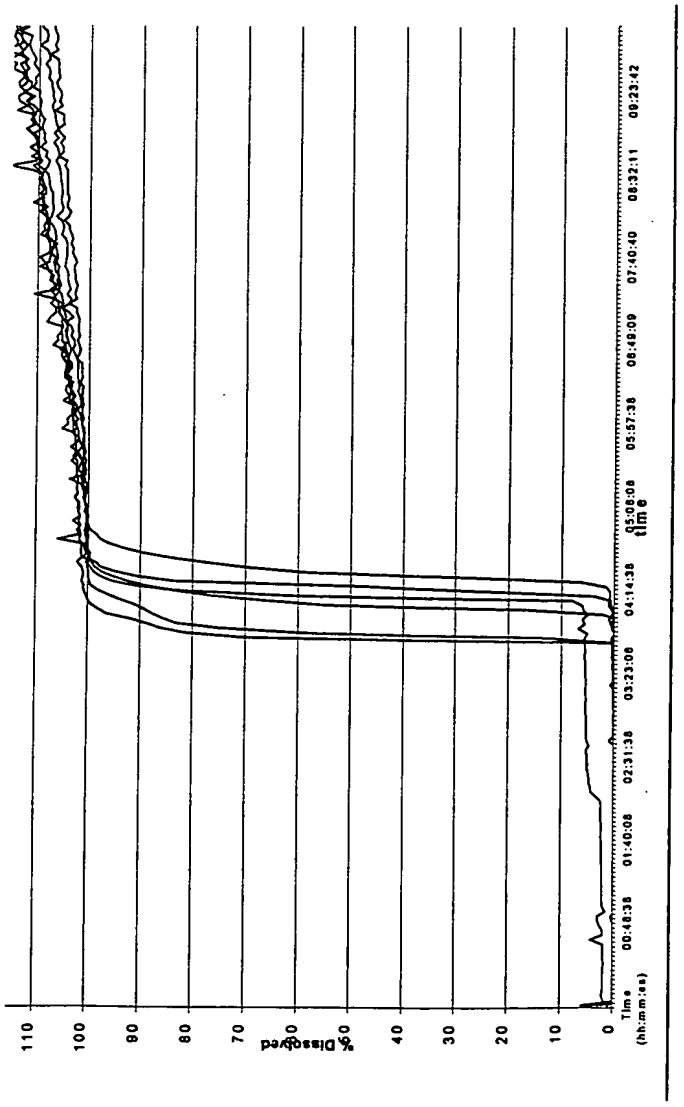
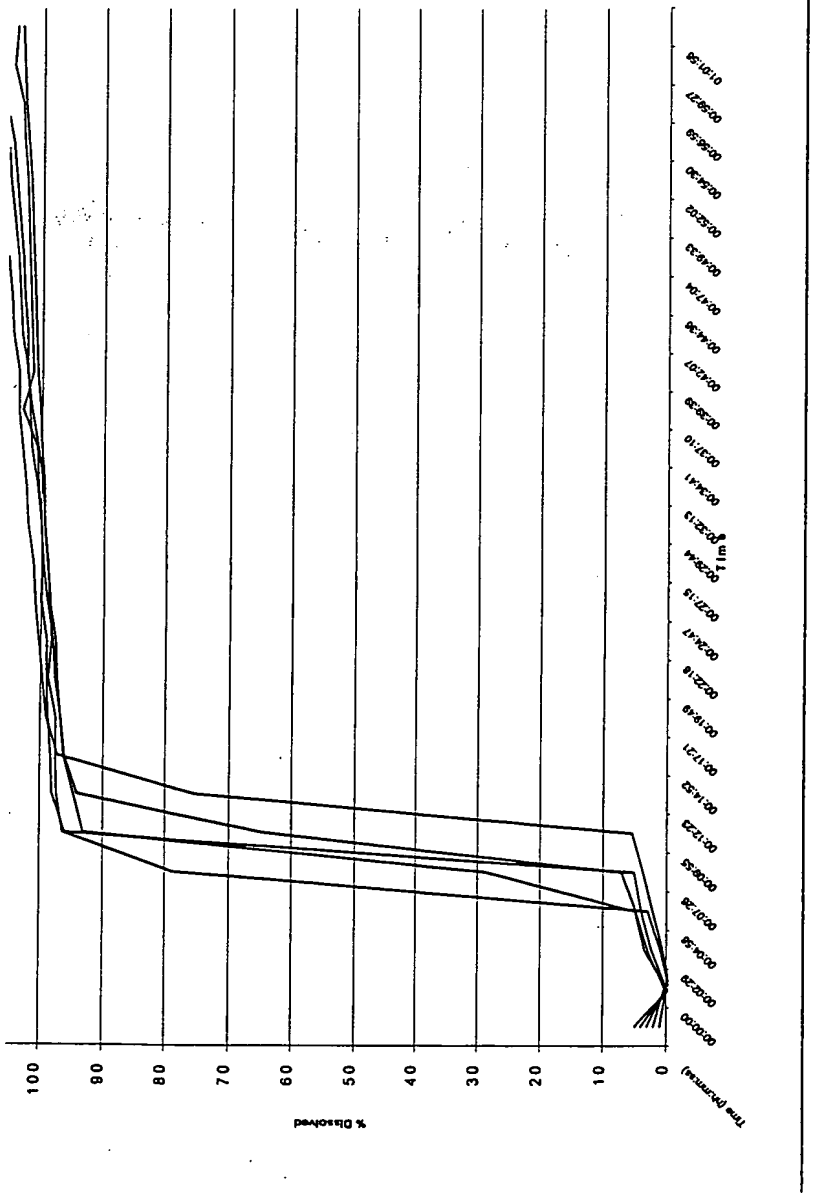

% Dissolved
110
100
90
80
70
60
50
40
30
20
10
0
Time
(hh:mm:ss)
00:48:36
01:40:08
02:31:38
03:23:06
04:14:38
05:06:08
05:57:36
06:49:09
07:40:40
08:32:11
09:23:42
Time

FIGURE 6


% Dissolved
100
90
80
70
60
50
40
30
20
10
0
Time (hh:mm:ss)
00:00:00
00:02:28
00:04:58
00:07:28
00:09:58
00:12:28
00:14:58
00:17:31
00:19:58
00:22:18
00:24:47
00:27:15
00:29:44
00:32:13
00:34:41
00:37:10
00:39:39
00:42:07
00:44:36
00:47:04
00:49:33
00:52:02
00:54:30
00:56:59
00:59:27
01:01:56